

**III. BIOCRYSTAL IS THE REAL PARTY IN INTEREST**

BioCrystal is the Assignee of the subject application and is the real party in interest.

**IV. RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**V. STATUS OF CLAIMS**

**A. The status of the claims in the application are:**

Claims 1-9, 18, 19, 29, 30, and 41-45 were cancelled.

Claims 10-17, 20-28, 31-40, and 46-62 are rejected under 35 U.S.C. § 112, second paragraph in the Office Action dated March 11, 2003.

**B. Claims pending are:**

Claims 10-17, 20-28, 31-40, and 46-62.

**VI. STATUS OF AMENDMENTS**

The Examiner stated in the Final Office Action dated March 11, 2003 that Applicant's Amendment A has been entered, however the substitute specification pages have not been entered.

Applicant wishes to thank the Examiner for the consideration given this case to date. Applicant has now had an opportunity to carefully consider the Examiner's action, and respectfully submits that the application, as amended, is now in condition for allowance. Presently, claims 10-17, 20-28, 31-40, and 46-62 are pending.

## **VII. SUMMARY OF INVENTION**

The application is directed to methods of detecting and assaying markers which indicate a disease condition consisting of multiple sclerosis (MS), a pro-MS immune response and a combination thereof.

In particular, the method is achieved because of a discovery that a combination of affinity ligands can be used in an immunoassay to generate one or more indicators that appear to differ in individuals having a disease condition selected from the group consisting of MS, a pro-MS immune response, and a combination thereof, as compared to a comparative values determined from healthy controls or in individuals having inflammatory diseases other than MS.

## **VIII. ISSUES**

Whether claims 10-17, 20-28, 31-40, and 46-62 are unpatentable under 35 U.S.C. § 112(¶ 2) as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention.

## **IX. ARGUMENT**

### **A. THE CLAIMS PATENTABLY POINT OUT AND DISTINCTLY CLAIM THE INVENTION AND THE REJECTIONS UNDER 35 U.S.C. § 112(¶ 2) SHOULD BE REVERSED**

The Office has rejected claims 11-17, 20-28, 31-40 and 46-62 under 35 U.S.C. § 112, second paragraph as being indefinite. The Office has maintained the position that the claims are confusing as to what is the recited marker and indicator, as stated in the First Office Action dated August 26, 2002. Specifically, the Office has taken the position that it is not clear if the marker

is present in the complexes or is the binding partner of the affinity ligand that comprises a detection reagent.

As indicated in Amendment A and Response to Office Action dated December 2, 2002, the marker as used in the claims is the entity being measured and compared against a reference value to determine the presence or absence of disease. For example, as taught in Example 1, the marker being measured is human IgG with an sTn epitope (Spec. pgs. 27-30). As the example illustrates, a sample is analyzed for the presence of the marker comprising human IgG and sTn epitope is employing a combination of affinity ligands comprising a murine anti- $\alpha$  (2,6) NeuAc antibody, which specifically binds to an epitope comprising free terminal alpha 2,6-linked sialic acid, and an anti-human IgG antibody, which specifically binds to an epitope comprising sTn. In this particular example, the murine anti- $\alpha$  (2,6) NeuAc antibody functions as the immobilized affinity ligand. Any sialocomplexes with terminal alpha 2,6-linked sialic acid necessarily become bound to the immobilized affinity ligand in the sample; the second affinity ligand comprising anti-human IgG antibody labeled with peroxidase is added, which will bind any IgG antibody, which, for example, corresponds to step (a) of claim 10. (See Spec. pg. 29). The value for the marker comprising human IgG and sTn epitope that may be present in the sample can then be measured and the measured value can be compared to a reference value, which corresponds to steps (b) and (c) of the claim 10. (See Spec. pg. 29 and Fig. 1). As illustrated by this example, the marker is present, if at all, in the complexes. That is, its presence and value is determined by measuring the binding of both of the two affinity ligands employed in step (a) of claim 10. It is clear that the affinity ligand having no detection reagent will bind to a particular component of the sialocomplex, if present. As the Specification teaches, this component may be a sialoadhesion, a glycolipid, or an antibody specifically bound to the sialocomplex. (Spec. pg.

27 -28). The affinity ligand with the detection reagent will bind to another component of the sialocomplex and will allow for a value of the marker to be determined or measured. (Spec. pg. 2-28).

The Office has also taken the position that the term “indicator” is unclear as used in the claims. In the First Office Action dated August 26, 2002, the Office asserted that it is unclear whether the indicator is (1) the same as the marker, or (2) a detectable entity, or (3) a nonphysical entity. Again, in Amendment A and Response to Office Action, the Applicant clearly explained that the term “indicator” as used in the claims refers to markers meeting a condition. For example, the condition includes the comparison between a reference value and a measured value of the marker.

The Office responded that “as far as the Examiner can ascertain from the response, Applicant considers that the word ‘indicator’ corresponds to what the examiner considered to be the ‘third interpretation’ of this word.” (Office Action page 2, last full paragraph). It is respectfully submitted that Applicant has not provided the Office with any more than one interpretation of the word “indicator,” which corresponds to the teachings of the specification. The Office suggested multiple interpretations of the term “indicator” in the first Office Action to which Applicant responded in the subsequent Amendment and Response. The Applicant has set forth and maintains that the term “indicator” as used in the claims refers to markers meeting a condition wherein if a difference does exist, the difference will indicate or be evidence of presence or absence of the disease condition. (See Spec. pg. 14-16).

The Office responded in the Final Office Action that “claim 10 remains confusing by virtue of reciting both comparing and difference in Step (c)” and further relies on the assertion that difference implies a subtraction whereas comparing implies a division to obtain a quotient.

While of dubious merit even in a mathematical context, the term “comparing” as used in the claims and taught by the Specification does not imply such a distinction. Rather, the comparison being performed in the claims involves determining whether or not any difference exists between two values. (See Examples 1-3 and Figs. 1-3). Any difference will then indicate the presence or absence of the disease. This difference can be obtained through subtraction, division, or any other method which would show a difference or lack thereof.

As the specification defines, “differs” and “difference” are a comparison between one or more markers or amounts (e.g., amount of sialocomplexes, or pattern of immunoreactivity when the sample is analyzed) measured in a sample and that of a comparative value (reference value or baseline value or a range of normal clinical values for the indicator that is established by clinical studies of apparently healthy individuals, the range of normal clinical values being referred to as a “reference value”). (See Spec. pg. 15-16). As the specification clearly and succinctly states, a difference involves a comparison.

Neither are the two terms are not inapposite, as the Office has asserted. To be sure, compare is “to examine (two or more objects, ideas, people, etc.) in order to note similarities and differences” Random House Dictionary, Unabridged 416 (2d ed. 1987). A difference is the “state or relation of being different; dissimilarity” and different is defined as “not alike in characteristics or quality; differing; dissimilar” Random House Dictionary, Unabridged 551-52 (2d ed. 1987). According to Webster’s Collegiate Dictionary, to compare is “to represent as similar; to examine the character or qualities of especially in order to discover resemblances or differences; to view in relation to.” Merriam-Webster’s Collegiate Dictionary 234 (10th ed. 1999). Difference is defined as “the degree of amount by which things differ in quality or measure.” Merriam-Webster’s Collegiate Dictionary 323 (10th ed. 1999). The ordinary

meanings of the terms clearly support the Applicant's use of both comparing and difference in the claims, as the terms, as illustrated by their definitions, encompass a broader, compatible function.

**X. CONCLUSION**

For the foregoing reasons, Applicant respectfully asserts that the case is now in a condition for allowance. The Commissioner is hereby authorized to charge any additional fees, or credit any overpayment to Deposit Account No. 02-2051, referencing Attorney Docket No. 26983-50.

Dated: 12 MAY 2003

Respectfully submitted,

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